PATENT
Docket No.: 19603/4542 (CRF D-3303-03)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Han et al.	Examiner: Sahar Javanmard
Serial No.	:	10/575,683	Art Unit: 1617
Cnfrm. No.	:	4626	
Filed	:	August 31, 2006	
For	:	TREATING AN INFLAMMATORY DISORDER OR INHIBITING RESPIRATORY BURST IN ADHERENT NEUTROPHILS WITH CHEMICAL INHIBITORS OF NEUTROPHIL ACTIVATION	

REQUEST FOR RECONSIDERATION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the June 15, 2009, office action, applicants respectfully request reconsideration.

Neutrophils are polymorphonuclear leukocytes (PMNs) of the blood that play a major role in almost all forms of acute inflammation and many forms of chronic inflammation, such as rheumatoid arthritis. When triggered, neutrophils secrete potent oxidants and proteases that contribute to inflammation but also help protect the host from infection. Neutrophils respond to soluble inflammatory mediators by migrating to the site of tissue injury and by ingesting and destroying invading pathogens and damaged tissue, leading, ultimately, to resolution and tissue repair. An inherent dilemma of anti-inflammatory therapy, the risk of impairing host defense, is particularly problematic with neutrophils.

To participate effectively in the inflammatory process, neutrophils must leave the bloodstream and migrate into the tissues. The initial step in this process is adherence to the vascular endothelium. Adherence of neutrophils to endothelium, their diapedesis from

venules into tissues, and their release of peptides, proteases, and reactive oxygen intermediates underlie both their killing of bacteria and their damage to tissues.

Full activation of neutrophils by soluble host products requires a binary signal. One part of the signal consists of integrin ligation during adherence to extracellular matrix. Simultaneously, a factor such as tumor necrosis factor (TNF), lymphotoxin, C5a, formylated peptides, macrophage inflammatory protein (MIP-1), granulocyte-specific colony stimulating factor (G-CSF), or granulocyte-macrophage-specific colony stimulating factor (GM-CSF), must engage its receptor(s) on the neutrophil. TNF has been studied extensively with respect to both the mechanisms by which it activates adherent neutrophils and the benefit of its neutralization in inflammatory disorders such as rheumatoid arthritis, ankylosing spondylitis, and Crohn's Disease.

Following adherence, the immune response of neutrophils involves chemotaxis, phagocytosis, and degranulation. Neutrophils sense and respond to gradients of activating agents (chemokines), which stimulate the neutrophil to move towards the gradient in a process known as chemotaxis. Activated neutrophils are also capable of phagocytosing, *i.e.*, engulfing foreign or damaged material, an important aspect of the inflammatory response. To engulf a particle, neutrophils extend pseudopodia, which engulf the offending material, trapping the material inside the cell in a compartment known as a phagosome. Cytoplasmic-bound granules, the primary and secondary granules of the neutrophil, which contain a multitude of effector proteins, fuse with the phagosome, placing effector proteins in direct contact with the ingested material. Components of the primary granules include lysozyme, which can digest the peptidoglycan component of most bacterial cell walls, and elastase, cathepsin G, defensins, bacterial permeability-increasing protein (BPI), and myeloperoxidase, which converts hydrogen peroxide generated by NADPH oxidase and hydrochloric acid to hypochlorous acid, all with inherent antibacterial activity. Among the proteins contained in the secondary granules are lactoferrin, an iron-binding protein with some antibacterial activity. The secondary granules also contain stored sources of CR3 and other receptors for neutrophil activation agents, as well as stored membrane components of NADPH oxidase. NADPH oxidase is a crucial component of the neutrophil host defense mechanism. This enzyme assembles on the phagosomal membrane to generate superoxide anion from molecular oxygen and free electrons. Superoxide is then converted to the toxic metabolite hydrogen peroxide by the actions of superoxide dismutase, or to hypochlorous

acid by the primary granule component myeloperoxidase. This ability to generate toxic oxygen metabolites is crucial to host defense against microbes.

The histotoxic impact of neutrophils is prominent in several inflammatory settings that are not thought to involve bacterial infection, such as rheumatoid arthritis, Crohn's Disease, and ischemia-perfusion syndrome, or in which neutrophil-mediated injury can occur at sites remote from invading bacteria, as in the acute respiratory distress and systemic inflammatory response syndromes. The stimuli that activate neutrophils in these settings are host-derived mediators (e.g., TNF), rather than bacteria themselves. What is needed is a method for inhibiting some inflammatory functions of activated neutrophils while sparing antimicrobial functions. Such a method would be particularly useful for preventing and treating inflammatory disorders related to respiratory burst in neutrophils mediated by effector proteins such as TNF.

The present invention is directed to overcoming these and other deficiencies in the art.

Enclosed please find a copy of Picciola et al., "Composti Eterociclici a Potenziale Attivita Antiinfiammatoria Contenenti il Residuo di un Acido 4-Amminofenilalcanoico," *Farmaco* 39:371-378 (1984), listed on the Information Disclosure Statement filed July 10, 2006, and which the U.S. Patent and Trademark Office ("PTO") has requested. This reference was cited in the International Search Report of the corresponding PCT application, and a copy should have been transferred to the PTO by the International Search Authority. Thus, as noted on page 2 of the outstanding office action, the instant submission of this reference is considered to have been a part of the IDS filed July 10, 2006, and no fee is due. Applicants respectfully request that the PTO sign and return the IDS filed July 10, 2006, acknowledging the consideration of this reference.

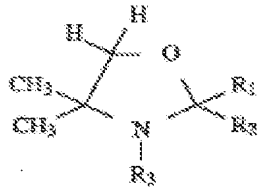
The rejection of claims 24 and 44 under 35 U.S.C. § 103(a) for obviousness over WO 03/024446 to Yamamoto ("Yamamoto") as evidenced by the Medilexicon medical dictionary (http://www.medilexicon.com/medicaldictionary.php?t=13063) ("Medilexicon") in view of U.S. Patent No. 5,462,946 to Mitchell ("Mitchell") is respectfully traversed.

Yamamoto discloses an oxidation stress inhibitor containing as the active ingredient a pyrazolone derivative or its pharmaceutically acceptable salt, and a method of measuring oxidation stress. Yamamoto also discloses the oxidation stress inhibitor is useful as a preventive remedy for various oxidation stress diseases, (*e.g.*, ischemic diseases and

various diseases depending thereon – *i.e.* cerebrovascular diseases (such as brain infarction and brain attack, brain hypofunction and vascular dementia caused thereby), various brain diseases in association with aging (such as cerebrovascular tissue lesion, various peripheral circulatory disorders based on cardiomuscular ischemia like cardiomuscular infarction and heart failure), liver failure, and diabetes).

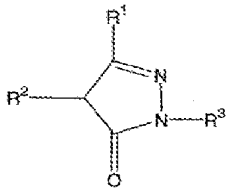
Medilexicon defines respiratory burst as "the marked increase in metabolic activity that occurs in phagocytes and certain other cells following binding of particles resulting in an increase in oxygen consumption, formation of superoxide anion, formation of hydrogen peroxide, and activation of the hexose monophosphate shunt."

Mitchell teaches a biologically compatible composition, containing an effective amount of a metal independent nitroxide compound of the formula:



and a pharmaceutically acceptable carrier. This composition is useful as an antioxidant capable of protecting cells, tissues, organs, and whole organisms against the deleterious effects of harmful oxygen-derived species generated during oxidative stress. Mitchell also teaches that free radicals and toxic oxygen-related species have been implicated in ischemia/reperfusion injury, and have long been thought to be important in neutrophil-mediated toxicity of foreign pathogens.

It is the position of the U.S. Patent and Trademark Office ("PTO") that Yamamoto's oxidation stress inhibitors have the formula (I):



(I)

or its pharmaceutically acceptable salt, wherein R^1 = H, aryl, C_{1-5} alkyl, C_{3-6} alkoxycarbonylalkyl; R^2 = H; R^3 = H, C_{1-5} alkyl, C_{5-7} cycloalkyl, C_{1-3} hydroxyalkyl, benzyl,

naphthyl, Ph optionally substituted. However, as the PTO acknowledges, Yamamoto fails to teach inhibiting respiratory burst, as recited in claims 24 and 44. The PTO cites Medilexicon for a definition of respiratory burst and further cites Mitchell for teaching that free radicals have been implicated in ischemia/reperfusion injury and have been important in neutrophil-mediated toxicity of foreign pathogens. Accordingly, the PTO asserts that it would have been obvious to one of skill in the art that the pyrazole compounds taught by Yamamoto would also be effective in treating respiratory burst as it relates to neutrophils. Further, based on Mitchell, the PTO asserts that it was known in the art that ischemic injuries are important in neutrophil-mediated toxicity of foreign pathogens. As a result, the PTO believes that the instant compounds would necessarily treat respiratory burst. Applicants respectfully disagree.

Initially, it should be noted that the PTO relies on more than the English translation of the abstract of Yamamoto (*i.e.*, the descriptions of R^1, R^2, and R^3 that are not found in the abstract), and the PTO has not provided a translation of the full text of Yamamoto. As stated in Manual of Patent Examining Procedure ("MPEP") § 706.02 (emphasis added):

> When an abstract is used to support a rejection, the evidence relied upon is the facts contained in the abstract, not additional facts that may be contained in the underlying full text document. Citation of and reliance upon an abstract without citation of and reliance upon the underlying scientific document is generally inappropriate where both the abstract and the underlying document are prior art. See *Ex parte Jones*, 62 USPQ2d 1206, 1208 (Bd. Pat. App. & Inter. 2001) (unpublished). To determine whether both the abstract and the underlying document are prior art, a copy of the underlying document must be obtained and analyzed. If the document is in a language other than English and the examiner seeks to rely on that document, *a translation must be obtained so that the record is clear as to the precise facts the examiner is relying upon in support of the rejectio*n.

Applicants' independent evaluation suggests that Yamamoto discloses: R^1 = H, aryl, $C_{1\text{-}5}$ alkyl, $C_{3\text{-}6}$ alkoxycarbonylalkyl; and R^2 = H, aryl-oxy, $C_{1\text{-}5}$alkyl, aryl mercaptos – *i.e.*, Yamamoto does not disclose phenyl specifically. Thus, it is unclear if Yamamoto teaches what the PTO asserts that it teaches and, for this reason alone, this rejection is improper and should be withdrawn.

However, Applicants also submit that there would have been no reason to combine the teachings of Yamamoto, Medilexicon, and Mitchell. In particular, Yamamoto

teaches a pyrazolone compound which inhibits oxidation stress, but fails to teach or in any way suggest inhibiting respiratory burst. While Medilexicon defines the term respiratory burst (as describing the formation of superoxide anion and hydrogen peroxide), this reference does not mention a method for inhibiting respiratory burst. In addition, although Mitchell teaches that free radicals are important in neutrophil-mediated toxicity of foreign pathogens, nowhere does Mitchell mention the term respiratory burst. Instead, Mitchell discusses the removal of foreign pathogens. Thus, one of skill in the art would have no reason to combine the teachings of Yamamoto, Medilexicon, and Mitchell.

Moreover, even if one of skill in the art would have combined these references (which Applicants submit that such a person would not have done), the combination of these references does not lead to the conclusion that the compounds recited in Yamamoto would treat respiratory bursts *without inhibiting neutrophil degranulation in or bacterial killing by neutrophils*, as recited in the present claims. The teaching of Mitchell that free radicals have been implicated in both ischemia and neutrophil-mediated toxicity of foreign pathogens would not lead to the conclusion that the compounds of Yamamoto (which are useful in treating ischemia) *would not inhibit* neutrophil degranulation in or bacterial killing by neutrophils. In fact, the combination of references suggested by the PTO teaches away from this conclusion (*i.e.*, that the compounds of Yamamoto *would affect* neutrophil degranulation in or bacterial killing by neutrophils). In addition, while Medilexicon defines the term respiratory burst, Medilexicon does not overcome these deficiencies in Yamamoto and Mitchell.

Further, MPEP § 2143 requires "a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable." Even if these references were combinable (which they are not), there is also no suggestion in Yamamoto, Medilexicon, or Mitchell that inhibition of respiratory burst *without inhibiting neutrophil degranulation in or bacterial killing by neutrophils* would be obtained.

Thus, for all of these reasons, the rejection of claims 24 and 44 under 35 U.S.C. § 103(a) for obviousness over these references is improper and should be withdrawn.

In view of all of the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: December 15, 2009

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